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WASHINGTON
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PARIS

DEC 17 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

SUITABILITY PETITION

This petition is submitted pursuant to 21 CFR parts 10.20 and 10.30, as provided for in 21 CFR 314.93 and Section 505(j)(2)(c) of the Federal Food, Drug and Cosmetic Act to request the Commissioner of the Food and Drug Administration to declare that the drug product Acyclovir Dispersible Tablets 200 mg are suitable for submission as an abbreviated new drug application (ANDA).

A. Action Requested

The petition is submitted for a change in dosage form of the drug product from "oral suspension" and "capsules" to "dispersible tablets". The listed drug product is Zovirax® oral suspension 200 mg/5 mL and Zovirax® capsules 200 mg manufactured by Glaxo Wellcome (Glaxo). Acyclovir will be marketed as dispersible tablets in a dosage strength of 200 mg. The drug, the route of administration and the recommendations for use are the same as the listed drug product. The proposed product would differ only in dosage form from Glaxo's marketed product.

The proposed drug product is expected to demonstrate bioequivalence to both 200 mg/5 mL suspension and 200 mg capsule dosage forms of the listed product which will be submitted at a later date.

B. Statement of Grounds

Dispersible tablet is presented for administration by dispersing a single tablet in a specified amount of water.

The new dosage form would be a better alternative to the oral suspension with regards to the following advantages:

Unit dose dispensing.
Convenience to the patient with respect to the administration during traveling.
Better precision of dosage over the traditional teaspoonful.
Ease of carrying.

99P-5452

CP 1

Additionally, dispersible tablets can also be a viable alternative to the capsule dosage form for the patients who have problems swallowing the solid oral dosage forms.

As the proposed product will differ only in dosage form, and the indications, strength, route of administration, intended patient population and recommendations for use remain the same as Glaxo's marketed product, therefore there will be no difference in the safety and efficacy of the proposed dispersible tablets.

A package insert of Glaxo's Zovirax® is attached along with the draft package insert of the proposed Acyclovir Dispersible Tablets.

C. **Pediatric Use Information**

As the package insert of Glaxo's Zovirax® oral suspension contains adequate dosing and administration information for the pediatric population, no additional studies are required.

D. **Environmental Impact**

An environmental assessment report on the action requested in this petition is not required under 21 CFR 25.24.

E. **Economic Impact**

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis if requested by the Agency.

F. **Certification**

The undersigned certifies that to the best of its knowledge, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Sincerely,

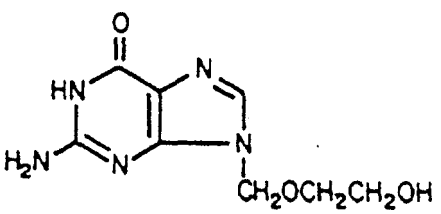
Nicholas M. Fleischer, R.Ph., Ph.D.
Director of Biopharmaceutics
THE WEINBERG GROUP INC.

ACYCLOVIR

DISPERSIBLE TABLETS

Rx only

Description: Acyclovir is an antiviral drug. Acyclovir dispersible tablets are formulations for oral administration, Each dispersible tablet contains 200 mg, 400 mg or 800 mg of acyclovir.
Inactive ingredients will be furnished when ANDA is submitted, since this is' proprietary information. The inactives are GRAS ingredients at the appropriate levels.



Acyclovir is a white to off-white crystalline powder with a molecular weight of 225.21, and formula $C_8H_{11}N_5O_3$. The maximum solubility in water at 37°C is 2.5 mg/mL. The pka's of acyclovir are 2.27 and 9.25.

VIROLOGY: Mechanism of Antiviral Action: Acyclovir is a synthetic purine nucleoside analogue with *in* vitro and *in vivo* inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV). In cell culture, acyclovir's highest antiviral activity is against HSV-1, followed in decreasing order of potency against HSV-2 and VZV.

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. *In vitro*, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in three ways: 1) competitive inhibition of viral DNA polymerase, 2) incorporation into and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral TK.

Antiviral Activities: The quantitative relationship between the in *vitro* susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virua sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 60% the growth of virus in cell *culture* (IC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC_{50} against herpes simplex virus isolates ranges from 0.02 to 13.6 mcg/mL for HSV-1 and from 0.01 to 9.9 mcg/mL for HSV-2. The IC_{50} for acyclovir against most laboratory strains and clinical isolator of VZV ranges from 0.12 to 10.8 mcg/mL. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a *mean* IC_{50} of 1.35 mcg/mL.

Drug Resistance: Resistance of VZV to antiviral nucleoside analogues can result from qualitative or quantitative changes in the viral TK or DNA polymerase. Clinical isolates of VZV with reduced susceptibility to acyclovir have been recovered from patients with AIDS. In these cases, TK-deficient mutants of VZV have been recovered.

Resistance of HSV to antiviral nucleoside analogues occurs by the same mechanisms as resistance to VZV. While most of the acyclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have also been isolated. TK-negative mutants may cause *severe* disease in immunocompromised patients. The possibility of viral resistance to acyclovir should be considered in patients who show poor clinical response during therapy.

CLINICAL PHARMACOLOGY: Pharmacokinetics: The pharmacokinetics of acyclovir after oral administration have been evaluated in healthy volunteers and in immunocompromised patients with herpes simplex or varicella-zoster virus infection. Acyclovir pharmacokinetic parameters are summarized in Table 1.

Table 1: Acyclovir Pharmacokinetic Characteristics (Range)

Parameter	Range
Plasma protein binding	9% to 33%
Plasma elimination half-life	2.5 to 3.3 hr
Average oral bioavailability	10% to 20%'

. Bioavailability decreases with increasing dose.

In one multiple-dose, cross-over study in healthy subjects (n=23), it was shown that increases in plasma acyclovir concentrations *were* less than dose proportional with increasing dose, as shbwn in Table 2. The decrease in bioavailability is a function of the dose and not the dosage form.

Table 2: Acyclovir Peak and Trough Concentrations at Steady State.

Parameter	200 mg	400 mg	800 mg
C^{ss}_{max}	0.83 mcg/mL	1.21 mcg/mL	1.61 mcg/mL
C^{ss}_{trough}	0.46 mcg/mL	0.63 mcg/mL	0.83 mcg/mL

There was no effect of food on the absorption of acyclovir (n=6); therefore, acyclovir capsules and tablets may be administered with or without food.

The only known urinary metabolite is 9-[(carboxymethoxy) methyllguanine.

Special Populations: ***Adults with Impaired*** **Renal** ***Function:*** The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function (see DOSAGE AND ADMINISTRATION).

Pediatrics: In general, the pharmacokinetics of acyclovir in pediatric patients is similar to that of adults. Mean half-life after oral doses of 300 mg/m² and 600 mg/m² in pediatric patients ages 7 months to 7 years was 2.6 hours (range 1.59 to 3.74 hours).

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase acyclovir half-life and systemic exposure. Urinary excretion and renal clearance were correspondingly reduced.

clinical trials: ***Initial Genital Herpes:*** Double-blind, placebo-controlled studies have demonstrated that orally administered acyclovir significantly reduced the duration of acute infection and duration of lesion healing. The duration of pain and new lesion formation was decreased in some patient groups.

Recurrent Genital Herpes: Double-blind, placebo-controlled studies in patients with frequent recurrences (six or more episodes per year) have shown that orally administered acyclovir given daily for 4 months to 10 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients.

In a study of patients who received acyclovir 400 mg twice daily for 3 years, 45%, 52%, and 63% of patients remained free of recurrences in the first, second and third years, respectively. Serial analyses of the S-month recurrence rates for the patients showed that 71% to 87% were recurrence-free in each quarter.

Herpes Zoster Infections: In a double-blind, placebo-controlled study of immunocompetent patients with localized cutaneous zoster infection, acyclovir (800 mg five times daily for 10 days) shortened the times to lesion scabbing, healing, and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation.

In a similar double-blind, placebo-controlled study, acyclovir (800 mg five times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia, or hyperesthesia).

Treatment was begun within 72 hours of rash onset and was most effective if started within the first 48 hours.

Adults greater than 50 years of age showed greater benefit.

Chickenpox: Three randomized, double-blind, placebo-controlled trials were conducted in 993 pediatric patients ages 2 to 18 years with chickenpox. All patients were treated within 24 hours after the onset of rash. In two trials, acyclovir was administered at 20 mg/kg four times daily (up to 3,200 mg per day) for 5 days. In the third trial, doses of 10, 15, or 20 m&were administered four times daily for 5 to 7 days. Treatment with acyclovir shortened the time to 50% healing, reduced the maximum number of lesions, reduced the median number of vesicles, decreased the median number of residual lesions on day 28, and decreased the proportion of patients with fever, anorexia, and lethargy by day 2. Treatment with acyclovir did not affect varicella-zoster virus-specific humoral or cellular immune responses at 1 month or 1 year following treatment.

INDICATIONS AND USAGE:

Herpes Zoster Infections: Acyclovir is indicated for the acute treatment of herpes zoster (shingles).

Genital Herpes: Acyclovir is indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes.

Chickenpox: Acyclovir is indicated for the treatment of chickenpox (varicella).

CONTRAINDICATIONS: Acyclovir is contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations.

WARNINGS: Acyclovir capsules and tablets are intended for oral ingestion only.

PRECAUTIONS: Dosage adjustment is recommended when administering Acyclovir to patients with renal impairment (See DOSAGE AND ADMINISTRATION), Caution should also be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction and/or the risk of reversible central nervous system symptoms such as those that have been reported in patients treated with intravenous acyclovir.

Infotmatlon for Patients: Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered acyclovir or they have any other questions.

Herpes Zoster: There are no data on treatment initiated more than ‘72 hours after onset of the zoster rash. Patients should be advised to initiate treatment as soon as possible after a diagnosis of herpes zoster.

Genital Herpes Infections: Patients should be informed that acyclovir is not a cure for genital herpes. There are no data evaluating whether acyclovir will prevent transmission of infection to others. Bocauee genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medial management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at tho first sign or symptom of an epiaode.

Chickenpox: Chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity. Adolescents and adults tend to have a more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course.

Drug Interactions: See CLINICAL PHARMACOLOGY: Pharmacokinetics.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally six times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally six times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (See CLINICAL PHARMACOLOGY, Pharmacokinetics).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. Maximum plasma concentrations were three to six times human levels in the mouse bioassay and one to two times human levels in rate bioassay.

Acyclovir was tested in 16 genetic toxicity assays. No evidence of mutagenicity was observed in four microbial assays. Acyclovir demonstrated mutagenic activity in two *in. vitro* cytogenetic assays (one mouse lymphoma cell line and human lymphocytes). No mutagenic activity was observed in five *in vitro* cytogenetic assays (three Chinese hamster ovary cell lines and two mouse lymphoma cell lines).

A positive result was demonstrated in one of two in *vitro* cell transformation assays, and morphologically transformed cells obtained in this assay formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. No mutagenic activity was demonstrated in another, possibly less sensitive, *in vitro* cell transformation assay.

Acyclovir was clastogenic in Chinese hamsters at 380 to 760 times human dose levels. In rats, acyclovir produced a non-significant increase in chromosomal damage at 62 to 125 times human levels. No activity was observed in a dominant lethal study in mice at 36 to 73 times human levels.

Acyclovir did not impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study, plasma levels were 9 to 18 times human levels, while in the rat study, they were 8 to 15 times human levels. At higher doses (50 mg/kg/day, s.c.) in rats and rabbits (11 to 22 and 16 to 31 times human levels, respectively) implantation efficacy, but not litter size, was decreased, in a rat peri- and post-natal study at 50 mg/kg/day, s.c., there was a statistically significant decrease in group mean numbers of corpea lutea, total implantation sites, and live fetuses.

No testicular abnormalities were seen in dogs given 50/mg/kg/day, i.v. for 1 month (21 to 41 times human levels) or in dogs given 60/mg/kg/day orally for 1 year (six to 12 times human levels). Testicular atrophy and aspermatogenesis were observed in rats and dogs at higher dose levels.

Pregnancy: *Teratogenic* Effects: Pregnancy Category B. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.), or rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test, rats were given three s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times-human levels. In this test, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.

There are no adequate and well-controlled studies in pregnant women. A prospective epidemiological registry of acyclovir use

during pregnancy has been ongoing since 1984. As of June 1996, outcomes of live births have been documented in 494 women exposed to systemic acyclovir during the first trimester of pregnancy. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged *from* 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir as high as 0.3 mg/kg/day. Acyclovir should be administered to a nursing mother with caution and only when indicated.

Geriatric **Use: Clinical** studies of acyclovir did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, and of concomitant disease or other drug therapy.

Pediatric Use: Safety and effectiveness *in* pediatric patients less than 2 years of age have not been adequately studied.

ADVERSE REACTIONS:

Herpes Simplex: ***Short-Term Administration:*** The most frequent adverse events reported during clinical trials of treatment of genital herpes with acyclovir 200 mg administered orally five times daily every 4 hours for 10 days were nausea and/or vomiting in 8 of 298 patient treatments (2.7%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Long-Term Administration: The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) two times daily for 1 year in 586 patients treated with acyclovir were nausea (4.8%) and diarrhea (2.4%). The 589 control patients receiving intermittent treatment of recurrences with acyclovir for 1 year reported diarrhea (2.7%), nausea (2.4%), and headache (2.2%).

Herpes Zoster: The most frequent adverse event reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir five times daily for 7 to 10 days in 323 patients was malaise (11.5%). The 323 placebo recipients reported malaise (11.1%).

Chickenpox: The most frequent adverse event reported during three clinical trials of treatment of chickenpox with oral acyclovir at doses of 10 to 20 mg/kg four times daily for 5 to 7 days or 800 mg four times daily for 5 days in 495 patients was diarrhea (3.2%) The 498 patients receiving placebo reported diarrhea (2.2%).

Observed During Clinical Practice: Based on clinical practice experience in patients treated with oral acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General: fever, headache, pain, peripheral edema, and rarely, anaphylaxis

Nervous: confusion, dizziness, hallucinations, paresthesia, seizure, somnolence (These symptoms may be marked, particularly in older adults.)

Digestive: diarrhea, elevated liver function tests, gastrointestinal distress, nausea

Hemic and Lymphatic: leukopenia, lymphadenopathy

Musculoskeletal: myalgia

Skin: alopecia, pruritus, rash, urticaria

Special Senses: visual abnormalities

Urogenital: elevated creatinine

OVERDOSAGE: Patients have ingested intentional overdoses of up to 100 capsules (20 g) of acyclovir, with no unexpected adverse effects. Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION:

Acute Treatment of Herpes Zoster: 800 mg every 4 hours orally, five times daily for 7 to 10 days.

Genital Herpes: ***Treatment of Initial Genital Herpes:*** 200 mg every 4 hours, five times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease: 400 mg two times daily for up to 12 months, followed by re-evaluation. Alternative regimens have included doses ranging Rom 200 mg three times daily to 200 mg five timer daily.

The frequency and severity of episodes of untreated 'genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of therapy with acyclovir.

Intermittent Therapy: 200 mg every 4 hours, five times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Treatment of **Chickenpox:** ***Children (2 years of age and older):*** 20 mg/kg per dose orally four times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and Children over 40 ***kg:*** 800 mg four times daily for 5 days.

Intravenous acyclovir is indicated for the treatment of varicella-zoster infections in immunocompromised patients.

When therapy is indicated, it should be initiated at the earliest sign or symptom of chickenpox. There is no information about the efficacy of therapy initiated more than 24 hours after onset of signs and symptoms.

Patients With Acute or Chronic Renal Impairment: In patients with renal impairment, the dose of acyclovir capsules and tablets should be modified as shown in Table 3:

Table 3: Dosage Modification for Renal Impairment

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73m²)	Adjusted Dose Regimen	
		Dose (mg)	Dosing Interval
200 mg every 4 hours	>10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
400 mg every 12 hours	>10	400	every 12 hours
	0-10	200	every 12 hours
800 mg every 4 hours	>25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

Hemodialysis: For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 6-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.

Peritoneal Dialysis: No supplemental dose appears to be necessary after adjustment of the dosing interval.

Acyclovir dispersible tablets should be dispersed in one teaspoonful of water before administration.

Bidequivalence of Dosage Forms: Acyclovir suspension was shown to be bioequivalent to acyclovir capsules (n-20) and one acyclovir 800 mg tablet was shown to be bioequivalent to four acyclovir 200 mg capsules (n=24).

HOW SUPPLIED: Acyclovir dispersible tablets 200 mg, 400 mg and 800 mg.

Package sizes to be determined.

Store at 15° to 25° C (59° to 77° F) and protect from moisture.

tion given twice a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. One 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy.

Pediatric Use: For patients 12 years of age and older, the dosage is the same as for adults. For patients 4 through 11 years of age, the dosage is one 4-mg ZOFRAN Tablet or one 4-mg ZOFRAN ODT Tablet or 5 mL (1 teaspoonful equivalent to 4 mg of ondansetron) of ZOFRAN Oral Solution given three times a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. One 4-mg ZOFRAN Tablet or one 4-mg ZOFRAN ODT Tablet or 5 mL (1 teaspoonful equivalent to 4 mg of ondansetron) of ZOFRAN Oral Solution should be administered three times a day (every 8 hours) for 1 to 2 days after completion of chemotherapy.

Use in the Elderly: The dosage is the same as for the general population.

Prevention of Nausea and Vomiting Associated With Radiotherapy, Either Total Body Irradiation, or Single High-Dose Fraction or Daily Fractions to the Abdomen: The recommended oral dosage is one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution given three times a day.

For total body irradiation, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered 1 to 2 hours before each fraction of radiotherapy administered each day.

For single high-dose fraction radiotherapy to the abdomen, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy.

For daily fractionated radiotherapy to the abdomen, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for each day radiotherapy is given.

Pediatric Use: There is no experience with the use of ZOFRAN Tablets, ZOFRAN ODT Tablets, or ZOFRAN Oral Solution in the prevention of radiation-induced nausea and vomiting in children.

Use in the Elderly: The dosage recommendation is the same as for the general population.

Postoperative Nausea and Vomiting: The recommended dosage is 16 mg given as two 8-mg ZOFRAN Tablets or two 8-mg ZOFRAN ODT Tablets or 20 mL (4 teaspoonfuls equivalent to 16 mg of ondansetron) of ZOFRAN Oral Solution 1 hour before induction of anesthesia.

Pediatric Use: There is no experience with the use of ZOFRAN Tablets, ZOFRAN ODT Tablets, or ZOFRAN Oral Solution in the prevention of postoperative nausea and vomiting in children.

Use in the Elderly: The dosage is the same as for the general population.

Dosage Adjustment for Patients With Impaired Renal Function: No specific studies have been conducted in patients with renal insufficiency.

Dosage Adjustment for Patients With Impaired Hepatic Function: In patients with severe hepatic insufficiency, clearance is reduced, apparent volume of distribution is increased with a resultant increase in plasma half-life, and bioavailability approaches 100%. In such patients, a total daily dose of 8 mg should not be exceeded.

HOW SUPPLIED

ZOFRAN Tablets, 4 mg (ondansetron HCl dihydrate equivalent to 4 mg of ondansetron), are white, oval, film-coated tablets engraved with "Zofran" on one side and "4" on the other in daily unit dose packs of 3 tablets (NDC 0173-0446-04), bottles of 30 tablets (NDC 0173-0446-00), and unit dose packs of 100 tablets (NDC 0173-0446-02).

ZOFRAN Tablets, 8 mg (ondansetron HCl dihydrate equivalent to 8 mg of ondansetron), are yellow, oval, film-coated tablets engraved with "Zofran" on one side and "8" on the other in daily unit dose packs of 3 tablets (NDC 0173-0447-04), bottles of 30 tablets (NDC 0173-0447-00), and unit dose packs of 100 tablets (NDC 0173X1447-02).

Store between 2° and 30°C 136' and 86°F). Protect from light. Store blisters and bottles in cartons.

ZOFRAN ODT Orally **Disintegrating Tablets, 4 mg (as 4 mg** ondansetron base) are white, round and plano-convex tablets with no marking on either side in "nit dose packs of 30 **tablets (NDC 0173-0569-00).**

ZOFRAN ODT Orally Disintegrating Tablets, 8 mg (as 8 mg ondansetron base) are white, round and plano-convex **tablets with no marking on either** side in unit dose packs **of** 30 tablets (NDC 0173-0570-003.

Store between 2° and 30°C (36° and 86°F).

ZOFRAN Oral Solution, a clear. colorless **to** light yellow liquid with a characteristic **strawberry** odor, contains **5** mg of ondansetron HCl dihydrate equivalent to 4 mg of ondansetron per 5 mL in amber glass bottles of 50 mL with child-resistant closures (NDC 0173-0489-00).

Store upright between 15° and 30°C (59° and 86°F). Protect from light. Store bottles upright in cartons.

ZOFRAN Tablets and Oral Solution:
Glaxo Wellcome Inc., Research Triangle Park, NC 27709
ZOFRAN ODT Orally Disintegrating Tablets:
Manufactured for Glaxo Wellcome Inc.
Research Triangle Park, NC 27709
by Scherer DDS
Blagrove, Swindon, Wiltshire, UK SN5 8RU
US Patent Nos. 4,695,578; 4,753,789; and 5,578,628

January 1999/RL-607

Shown in Product Identification Guide, page 316

ZOVIRAX® ℞
[zō vī'rax]
(acyclovir)
Capsules

ZOVIRAX® ℞
(acyclovir)
Tablets

ZOVIRAX® ℞
(acyclovir)
Suspension

D - O N

ZOVIRAX is the **brand** name for **acyclovir,** an **antiviral drug. ZOVIRAX Capsules, Tablets,** and **Suspension are** formulations **for oral administration. Each capsule** of **ZOVIRAX contains 200 mg of acyclovir and the inactive ingredients corn starch, lactose, magnesium stearate; and sodium lauryl sulfate. The capsule shell consists of gelatin, FD&C Blue No. 2, and titanium dioxide. May contain one or m ore parabens. Printed with edible black ink.**

Each 800-mg tablet of ZOVIRAX contains 800 mg of acyclovir and the inactive **ingredients FD&C** Blue No. 2, **magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.**

Each 400-mg tablet of ZOVIRAX contains 400 **mg** of **acyclovir and the inactive ingredients magnesium stearate, microcrystalline cellulose, povidone, and** sodium **starch glycolate.**

Each teaspoonful (5 mL) of ZOVIRAX Suspension contains 200 mg of **acyclovir** and the **inactive ingredients methylparaben** 0.1% and **propylparaben 0.02%** (added **as preservatives), carboxymethylcellulose sodium, flavor, glycerin, microcrystalline cellulose, and sorbitol.**

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H***-purin-6-one.**

Acyclovir is a **white, crystalline** powder **with** the **molecular formula $C_8H_{11}N_5O_3$** and **a** molecular weight of 225. **The maximum solubility in water at 37°C is 2.5 mg/mL.** *The* **pka's of acyclovir are 2.27 and 9.25.**

VIROLOGY

Mechanism of Antiviral Action: Acyclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and **varicella-zoster** virus **(VZV).** In **cell culture, acyclovir's highest antiviral** activity is against **HSV-1,** followed in **decreasing** order of **potency against** HSV-2 and VZV.

The inhibitory **activity** of **acyclovir** is highly selective due to **its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate** by **cellular guanylate kinase and into triphosphate** by a **number** of **cellular** enzymes. In **vitro,** acydovir **triphosphate** steps **replication of** herpes **viral** DNA **This** is **accomplished** in **three ways: 1)** competitive inhibition of **viral** DNA **polymerase, 2) incorporation** into and termination of the growing **viral DNA chain,** and **3)** inactivation of the **viral** DNA polymer**ase.** The greater antiviral activity of acyclovir against **HSV** compared to VZV is due to its more **efficient phosphorylation by the viral TK.**

Antiviral Activities: The quantitative **relationship** between **be in vitro** susceptibility **of herpes** viruses **to antivirals** and **the clinical response to** therapy has not been established in **humans,** and **virus sensitivity testing has** not been **standardized.** Sensitivity testing results. expressed as the **concentration** of **drug required to inhibit by** 50% the **growth** of **virus in** cell culture (IC_{50}), vary greatly depending upon a **number** of factors Using plaque-reduction assays, the IC_{50} **against** herpes simplex virus **isolates** ranges **from** 0.02 to **13.5 mcg/mL for HSV-1** and **from** 0.01 **to** 9.9 **mcg/mL** for **HSV-2.** The IC, **for** acyclovir against most **laboratory strains** and **clinical** isolates **of VZV ranges from** 0.12 to 10.8 mcg/mL. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a **mean** IC_{50} of 1.35 **mcg/mL. Drug** Resistance: Resistance of **VZV to** antiviral **nucleoside analogues can** result **from** qualitative or **quantitative changes** in the viral TK or DNA **polymerase.** Clinical isolates of **VZV** with reduced susceptibility **to** acyclovir have been **recovered from** patients with AIDS. In these cases, **TK-deficient** mutants of **VZV** have been recovered.

Resistance of HSV **to** antiviral nucleoside **analogues** occurs **by the same** mechanisms **as** resistance to VZV. While most of the acyclovir-resistant mutants isolated thus far from **immunocompromised** patients have been found to be **TK-deficient mutants,** other **mutants** involving the **viral** TK gene **(TK** partial and TK **altered) and** DNA **polymerase** have **also** been isolated. **TK-negative** mutants may cause severe disease in **immunocompromised** patients. The possibility of viral resistance **to acyclovir** should **be** considered in patients who show poor **clinical** response **during** therapy.

CLINICAL PHARMACOLOGY

Pharmacokinetics: The **pharmacokinetics** of **acyclovir after** oral **administration** have **been evaluated** in healthy **volunteers and in immunocompromised patients with herpes simplex or varicella-zoster virus infection. Acyclovir pharmacokinetic parameters are summarized in Table 1.**

Table 1: Acyclovir Pharmacokinetic Characteristics (Range)

Parameter	Range
Plasma protein binding	**9% to 33%**
Plasma **elimination half-life**	*2.6 to 3.3* hr
Average **oral bioavailability**	10% **to 20%***

*** Bioavailability decreases with increasing dose.**

In one multiple-dose, cross-over study in healthy subjects (n = 23), it was shown that increases in plasma acyclovir concentrations were less than dose proportional with increasing dose, as shown in Table 2. The decrease in bioavailability is a function of the dose and not the dosage form.

Table 2: Acyclovir Peak and Trough Concentrations at Steady State

Parameter	200 mg	400 mg	800 mg
C_{max}^{ss}	0.83 mcg/mL	1.21 mcg/mL	1.61 mcg/mL
C_{trough}^{ss}	0.46 mcg/mL	0.63 mcg/mL	0.83 mcg/mL

There was no effect of food on the absorption of acyclovir (n = 6); therefore ZOVIRAX Capsules, Tablets, and **Suspension may be administered with or without food.**

The only known **urinary metabolite** is **9-[(carboxymethoxy)methyl]guanine.**

Special Populations: *Adults with Impaired Renal Function:* **The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adustment is recommended for patients with reduced renal function bee DOSAGE AND ADMINISTRATION).**

Pediatrics: **In general, the pha[redacted]tics of acyclovir in pediatric patients is similar to that of adults. Mean half-life after oral doses of 300 mg/m² and 600 mg/m² in pediatric patients ages** *7 month to 7* **years** *was 2.6* hours **(range** 1.69 **to** *3.74* **hours).**

Drug Interactions: Coad[redacted]ion of probenecid with intravenous acyclovir has been shown to increase acyclovir half-life and systemic exposure. Urinary excretion and renal clearance were correspondingly reduced.

Clinical Trials: *Initial Genital Herpes:* **Double-blind, placebo-controlled studies have demo&ted that orally administered ZOVIRAX significantly** reduced the **duration of acute infection and duration of l&ion healing. The duration of pain and new lesion formation was decreased in some patient groups.**

Recurrent Genital Herpes: Double-blind, **placebo-controlled studies** in patients with frequent **recurrences** (six **or more episodes** per year) **have** shown that orally **administered ZOVIRAX** given daily for 4 months to 10 years prevented or reduced the frequency **and/or** severity of **recurrences** in **[redacted]p-eater** than 95% of patients.

In a study of patients who received ZOVIRAX **400 mg** twice **daily** for 3 years, **45%,** 526, and 63% of patients remained **free** of recurrences in the **first, second,** and third years, **respectively.** Serial analyses of the **3-month** recurrence rates for the patients showed that 71% **to** 87% were recurrence-**free** in **each** quarter.

Herpes Zoster Infections: In a double-blind, placebo-controlled study of **immunocompetent** patients with localized **cutaneous zoster** infection, ZOVIRAX **(800 mg five** times daily for 10 days) shortened the times to lesion scabbing. **healing,** and **complete** cessation of **pain,** and reduced the **duration of** viral **shedding** and the **duration** of new lesion formation.

In a similar double-blind, placebo-controlled study, ZOVIRAX **(800** mg five times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and **reduced** the prevalence of localized **zoster-associated neurologic** symptoms (paresthesia, dysesthesia. or **hyperesthesia).**

Treatment was begun within 72 hours of rash onset **and** was most effective if started within the first 48 hours.

Adults greater than 50 years of age showed greater benefit.

Chickenpox: Three randomized. double-blind, placebo controlled trials were conducted in 993 pediatric patients ages

2 to 18 years with chickenpox. All patients were treated within 24 hours after the onset of rash. In two trials, ZOVIRAX was administered at 20 mg/kg four times daily (up to 3200 mg per day) for 5 days. In the third trial, doses of 10, 15, or 20 mg/kg were administered four times daily for 5 to 7 days. Treatment with ZOVIRAX shortened the time to 50% healing, reduced the maximum number of lesions, reduced the median number of vesicles, decreased the median number of residual lesions on day 28, and decreased the proportion of patients with fever, anorexia, and lethargy by day 2. Treatment with ZOVIRAX did not affect varicella-zoster virus-specific humoral or cellular immune responses at 1 month or 1 year following treatment.

INDICATIONS AND USAGE

Herpes Zoster Infections: ZOVIRAX is indicated for the acute treatment of herpes zoster (shingles).

Genital Herpes: ZOVIRAX is indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes.

Chickenpox: ZOVIRAX is indicated for the treatment of chickenpox (varicella).

CONTRAINDICATIONS

ZOVIRAX is contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations.

WARNINGS

ZOVIRAX Capsules, Tablets, and Suspension are intended for oral ingestion only.

PRECAUTIONS

Dosage adjustment is recommended when administering ZOVIRAX to patients with renal impairment (see DOSAGE AND ADMINISTRATION). Caution should also be exercised when administering ZOVIRAX to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction and/or the risk of reversible central nervous system symptoms such as those that have been reported in patients treated with intravenous acyclovir.

Information for Patients: Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered ZOVIRAX, or they have any other questions.

Herpes Zoster: There are no data on treatment initiated more than 72 hours after onset of the zoster rash. Patients should be advised to initiate treatment as soon as possible after a diagnosis of herpes zoster.

Genital Herpes Infections: Patients should be informed that ZOVIRAX is not a cure for genital herpes. There are no data evaluating whether ZOVIRAX will prevent transmission of infection to others. Because genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at the first sign or symptom of an episode.

Chickenpox: Chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity. Adolescents and adults tend to have more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course.

Drug Interactions: See CLINICAL PHARMACOLOGY: Pharmacokinetics.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally six times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally six times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see Pharmacokinetics).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There wan no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. Maximum plasma concentrations were three to six times hums" levels in the mouse bioassay and one to two times human levels in the rat bioassay.

Acyclovir was tested in 16 genetic toxicity assays. No evidence of mutagenicity was observed in four microbial assays. Acyclovir demonstrated mutagenic activity in two in vitro cytogenetic assays (one mouse lymphoma cell line and human lymphocytes). No mutagenic activity was observed in five in vitro cytogenetic assays (three Chinese hamster ovary cell lines and two mouse lymphoma cell lines).

A positive result was demonstrated in one of two in vitro cell transformation assays, and morphologically transformed cells obtained in this assay formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. No mutagenic activity was demonstrated in another. possibly less sensitive. in vitro cell transformation assay.

Acyclovir was clastogenic in Chinese hamsters at 380 to 760 times human dose levels. In rats. acyclovir produced a non-significant increase in chromosomal damage at 62 to 125 times human levels. No activity was observed in a dominant lethal study in mice at 36 to 73 times human levels.

Acyclovir did not impair fertility or reproduction in mice (450 mg/kg per day, PO) or in rats (25 mg/kg per day, SC). In the mouse study, plasma levels were 9 to 18 times human levels, while in the rat study, they were 8 to 15 times human levels. At higher doses (50 mg/kg per day, SC) in rats and rabbits (11 to 22 and 16 to 31 times human levels, respectively) implantation efficacy, but not litter size, was decreased. In a rat peri- and post-natal study at 50 mg/kg per day, SC, there was a statistically significant decrease in group mean numbers of corpora lutea, total implantation sites, and live fetuses.

No testicular abnormalities were seen in dogs given 50 mg/kg per day, IV for 1 month (21 to 41 times human levels) or in dogs given 60 mg/kg per day orally for 1 year (six to 12 times human levels). Testicular atrophy and aspermatogenesis were observed in rats and dogs at higher dose levels.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B. Acyclovir was not teratogenic in the mouse (450 mg/kg per day, PO), rabbit (50 mg/kg per day, SC and IV), or rat (50 mg/kg per day, SC). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a nonstandard test, rats were given three SC doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. In this test, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.

There are no adequate and well-controlled studies in pregnant women. A prospective epidemiologic registry of acyclovir use during pregnancy has collected data since June 1984. As of December 1997, outcomes of live births have been documented in 552 women exposed to systemic acyclovir during the first trimester of pregnancy. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for specific defects or to permit definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Acyclovir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of ZOVIRAX and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir as high as 0.3 mg/kg per day. ZOVIRAX should be administered to a nursing mother with caution and only when indicated.

Geriatric Use: Clinical studies of ZOVIRAX did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, and of concomitant disease or other drug therapy.

Pediatric Use: Safety and effectiveness in pediatric patients less than 2 years of age have not been adequately studied.

ADVERSE REACTIONS

Herpes Simplex: ***Short-Term Administration:*** The most frequent adverse events reported during clinical trials of treatment of genital herpes with ZOVIRAX 200 mg administered orally five times daily every 4 hours for 10 days were nausea and/or vomiting in 8 of 298 patient treatments (2.7%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Long-Term Administration: The mast frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200-mg capsules) two times daily for 1 year in 586 patients treated with ZOVIRAX were nausea (4.8%) and diarrhea (2.4%). The 589 control patients receiving intermittent treatment of recurrences with ZOVIRAX for 1 year reported diarrhea (2.7%), nausea (2.4%), and headache (2.2%).

Herpes Zoster: The most frequent adverse event reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral ZOVIRAX five times daily for 7 to 10 days in 323 patients was malaise (11.5%). Tbe 323 placebo recipients reported malaise (11.1%).

Chickenpox: The most frequent adverse event reported during three clinical trials of treatment of chickenpox with oral ZOVIRAX at doses of 10 to 20 mg/kg four times daily for 5 to 7 days or 800 mg four times daily for 5 days in 495 patients was diarrhea (3.2%). The 498 patients receiving placebo reported diarrhea (2.2%).

Table 3: Dosage Modification for Renal Impairment

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73 m^2)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval
200 mg every 4 hours	>10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
400 mg every 12 hours	>10	400	every 12 hours
	0–10	200	every 12 hours
800 mg every 4 hours	>25	800	every 4 hours, 5x daily
	10–25	800	every 8 hours
	0–10	800	every 12 hours

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of acyclovir (ZOVIRAX). Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to ZOVIRAX.

General: Fever, headache, pain, peripheral edema, and rarely, anaphylaxis.

Nervous: Confusion, dizziness, hallucinations, paresthesia, seizure, somnolence (These symptoms may be marked, particularly in older adults.)

Digestive: Diarrhea, elevated liver function tests, gastrointestinal distress, nausea.

Hemic and Lymphatic: Leukopenia, lymphadenopathy.

Musculoskeletal: Myalgia.

Skin: Alopecia, erythema multiforme, pruritus, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria.

Special Senses: Visual abnormalities.

Urogenital: Elevated creatinine.

OVERDOSAGE

Patients have ingested intentional overdoses of up to 100 capsules (20 g) of ZOVIRAX, with no unexpected adverse effects. Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

Acute Treatment of Herpes Zoster: 800 mg every 4 hours orally, five times daily for 7 to 10 days.

Genital Herpes: ***Treatment of Initial Genital Herpes:*** 200 mg every 4 hours, five times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease: 400 mg two times daily for up to 12 months, followed by re-evaluation. Alternative regimens have included doses ranging from 200 mg three times daily to 200 mg five times daily. The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of therapy with ZOVIRAX.

Intermittent Therapy: 200 mg every 4 hours, five times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Treatment of Chickenpox: ***Children (2 years of age and older):*** 20 mg/kg per dose orally four times daily (80 mg/kg per day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and Children over 40 kg: 800 mg four times daily for 5 days.

Intravenous ZOVIRAX is indicated for the treatment of varicella-zoster infections in severely immunocompromised patients.

When therapy is indicated, it should be initiated at the earliest sign or symptom of chickenpox. There is no information about the efficacy of therapy initiated more than 24 hours after onset of signs and symptoms.

Patients With Acute or Chronic Renal Impairment: I" patients with renal impairment, the dose of ZOVIRAX Capsules, Tablets. or Suspension should be modified as shown in Table 3:

(See table 3 above)

Hemodialysis: For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a B-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.

Continued OR next page

This product information is based on labeling in effect on June 10, 1999. For further information, contact via direct mail, phone. or web site Medical Information: Glaxo Wellcome Inc., PO Box 13398. Research Triangle Park, NC 27709. Healthcare Professionals (Medical Information): 800-334-0089 Patients (Customer Response Center): 888-TALK2GW (1-888-825-5249) GlaxoWellcome Corporate Web Site: www.glaxowellcome.com

Peritoneal Dialysis: No supplemental dose appears to be necessary after adjustment of the dosing interval.

Bioequivalence of Dosage Forms: ZOVIRAX Suspension was shown to be bioequivalent to ZOVIRAX Capsules (n = 20) and one ZOVIRAX 800-mg tablet was shown to be bioequivalent to four ZOVIRAX 200-mg capsules (n = 24).

HOW SUPPLIED

ZOVIRAX Capsules (blue, opaque cap and body) containing 200 mg acyclovir and printed with "Wellcome ZOVIRAX 200"—Bottle of 100 (NDC 0173-0991-55) and unit dose pack of loo (NDC 0173-0991-56).

Store at 15° to 25°C (59° to 77°F) and protect from moisture.

ZOVIRAX Tablets (light blue, oval) containing 800 mg acyclovir and engraved with "ZOVIRAX 800"—Bottle of 100 (NDC 0173-0945-55) and unit dose pack of 100 (NDC 0173-0945-56).

Store at 15° to 25°C (59° to 77°F) and protect from moisture.

ZOVIRAX Tablets (white, shield-shaped) containing 400 mg acyclovir and engraved with "ZOVIRAX" on one side and a triangle on the other side—Bottle of 100 (NDC 0173-0949-55).

Store at 15° to 25°C (59° to 77°F) and protect from moisture.

ZOVIRAX Suspension (off-white, banana-flavored) containing 200 mg acyclovir in each teaspoonful (5 mL)—Bottle of 1 pint (473 mL) (NDC 0173-0953-96).

Store at 15° to 25°C (59° to 77°F).

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

January 1999/RL-670

Shown in Product Identification Guide, page 316

ZOVIRAX® ℞
[zō-vī 'răx]
(acyclovir)
Ointment 5%

DESCRIPTION

ZOVIRAX is the brand name for acyclovir, an antiviral drug active against herpes viruses. ZOVIRAX Ointment 5% is a formulation for topical administration. Each gram of ZOVIRAX Ointment 5% contains 50 mg of acyclovir in a polyethylene glycol (PEG) base.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one.

Acyclovir is a white, crystalline powder with a molecular weight of 225 daltons, and a maximum solubility in water of 1.3 mg/mL.

CLINICAL PHARMACOLOGY

Acyclovir is a synthetic acyclic purine nucleoside analogue with in vitro inhibitory activity against Herpes simplex types 1 and 2 (HSV-1 and HSV-2), varicella-zoster, Epstein-Barr, and cytomegalovirus. In cell cultures, the inhibitory activity of acyclovir for Herpes simplex virus is highly selective. Cellular thymidine kinase does not effectively utilize acyclovir as a substrate. Herpes simplex virus-coded thymidine kinase, however, converts acyclovir into acyclovir monophosphate, a nucleotide. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.[1] Acyclovir triphosphate interferes with Herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir triphosphate also inhibits cellular a-DNA polymerase but to a l-degree. In vitro. acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular α-DNA polymerase.[2] When incorporation occurs, the DNA chain is terminated.[3] Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic in vitro for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular α-DNA polymerase is less sensitive to the effects of the active form. The relationship between in vitro susceptibility of Herpes simplex virus to antiviral drugs and clinical response has not been established. The techniques and cell culture types used for determining in vitro susceptibility may influence the results obtained. Using a quantitative assay to determine the acyclovir concentration producing 50% inhibition of viral cytopathic effect (ID_{50}), 28 HSV-1 clinical isolates had a mean ID_{50} of 0.11 mcg/mL and 32 HSV-2 clinical isolates had a mean ID_{50} of 0.46 mcg/mL.* Results from other studies using different assays have yielded mean ID_{50} values for clinical HSV-1 isolates of 0.018. 0.03. and 0.049 mcg/mL and for clinical HSV-2 isolates of 0.027. 0.36. end 0.03 *mcg/mL respectively.*[4,5,6]

Two clinical pharmacology studies were performed with ZOVIRAX Ointment 5% in adult immunocompromised patients at risk of developing mucocutaneous Herpes simplex virus infections or with localized varicella-zoster infections. These studies were designed to evaluate the dermal tolerance, systemic toxicity, and percutaneous absorption of acyclovir.

In one of these studies, which included 16 inpatients, the complete ointment or its vehicle were randomly administered in a dose of l-cm strips (25 mg acyclovir) four times a day for 7 days to an intact skin surface area of 4.5 square inches. No local intolerance, systemic toxicity, or contact dermatitis were observed. In addition, no drug was detected in blood and urine by radioimmunoassay (sensitivity, 0.01 mcg/mL).

The other study included 11 patients with localized varicella-zoster. In this uncontrolled study, acyclovir was detected in the blood of nine patients and in the urine of all patients tested. Acyclovir levels in plasma ranged from <0.01 to 0.28 mcg/mL in eight patients with normal renal function, and from <0.01 to 0.78 mcg/mL in one patient with impaired renal function. Acyclovir excreted in the urine ranged from <0.02% to 9.4% of the daily dose. Therefore, systemic absorption of acyclovir after topical application is minimal.

INDICATIONS AND USAGE

ZOVIRAX (acyclovir) Ointment 5% is indicated in the management of initial herpes genitalis and in limited nonlife-threatening mucocutaneous Herpes simplex virus infections in immunocompromised patients. In clinical trials of initial herpes genitalis, ZOVIRAX Ointment 5% has shown a decrease in healing time and, in some cases, a decrease in duration of viral shedding and duration of pain. In studies in immunocompromised patients with mainly herpes labialis, there was a decrease in duration of viral shedding and a slight decrease in duration of pain.

By contrast, in studies of recurrent herpes genitalis and of herpes labialis in nonimmunocompromised patients, there was no evidence of clinical benefit; there was some decrease in duration of viral shedding.

Diagnosis: Whereas cutaneous lesions associated with Herpes simplex infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may assist in the diagnosis.[7] Positive cultures for Herpes simplex virus offer a reliable means for confirmation of the diagnosis. In genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases.

CONTRAINDICATIONS

ZOVIRAX Ointment 5% is contraindicated for patients who develop hypersensitivity or chemical intolerance to the components of the formulation.

WARNINGS

ZOVIRAX Ointment 5% is intended for cutaneous use only and should not be used in the eye.

PRECAUTIONS

General: The recommended dosage, frequency of applications, and length of treatment should not be exceeded (see DOSAGE AND ADMINISTRATION). There exist no data which demonstrate that the use of ZOVIRAX Ointment 5% will either prevent transmission of infection to other persons or prevent recurrent infections when applied in the absence of signs and symptoms. ZOVIRAX Ointment 5% should not be used for the prevention of recurrent HSV infections. Although clinically significant viral resistance associated with the use of ZOVIRAX Ointment 5% has not been observed, this possibility exists.

Drug Interactions: Clinical experience has identified no interactions resulting from topical or systemic administration of other drugs concomitantly with ZOVIRAX Ointment 5%.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of 50, 150, and 450 mg/kg per day given by gavage. These studies showed no statistically significant difference in the incidence of benign and malignant tumors produced in drug-treated as compared to control animals, nor did acyclovir induce the occurrence of tumors earlier in drug-treated animals as compared to controls. In two in vitro cell transformation assays, used to provide preliminary assessment of potential oncogenicity in advance of these more definitive lifetime bioassays in rodents, conflicting results were obtained. Acyclovir was positive at the highest dose used in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative in another transformation system.

No chromosome damage was observed at maximum tolerated parenteral doses of 100 mg/kg acyclovir in rats or Chirme hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters. In addition. no activity was found in a dominant lethal study in mice. In nine of 11 microbial and mammalian cell assays. no evidence of mutagenicity was observed. In two mammalian cell assays (human lymphocytes and L5178Y mouse lymphoma cells in vitm). positive response for mutagenicity and chromosomal damage occurred, but only at concentrations at least 1000 times the plasma levels achieved in humans following topical application.

Acyclovir does not impair fertility or reproduction in mica at oral doses up to 450 mg/kg per day or in rata at subcutaneous doses up to 25 m&g per day. In rabbits given a high dose of acyclovir (50 mg/kg per day, SC). there was a statistically significant decrease in implantation efficiency.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg per day, PO). rabbit (50 mg/kg per day, SC and IV) or in standard tests in the rat (50 mg/kg per day, SC). In a nonstandard test in rats. fetal abnormalities, such as head and tail anomalies, were observed following subcutaneous administration of acyclovir at very high doses associated with toxicity to the maternal rat. The clinical relevance of these findings is uncertain.* There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether topically applied acyclovir is excreted in breast milk. After oral administration of ZOVIRAX, acyclovir concentrations have been documented in breast milk in two women and ranged from 0.6 to 4.1 times the corresponding plasma levels.[9,10] Caution should be exercised when ZOVIRAX Ointment is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Because ulcerated genital lesions are characteristically tender and sensitive to any contact or manipulation, patients may experience discomfort upon application of ointment. In the controlled clinical trials, mild pain (including transient burning and stinging) was reported by 103 (28.3%) of 364 patients treated with acyclovir and by 115 (31.1%) of 370 patients treated with placebo; treatment was discontinued in two of these patients. Other local reactions among acyclovir-treated patients included pruritus in 15 (4.1%), rash in one (0.3%), and vulvitis in one (0.3%). Among the placebo-treated patients, pruritus was reported by 17 (4.6%) and rash by one (0.3%).

In all studies, there was no significant difference between the drug and placebo group in the rate or type of reported adverse reactions nor were there any differences in abnormal clinical laboratory findings.

Observed During Clinical Practice: Based on clinical practice experience in patients treated with ZOVIRAX Ointment in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General: Edema and/or pain at the application site
Skin: Pruritus, rash

OVERDOSAGE

Overdosage by topical application of ZOVIRAX Ointment 5% is unlikely because of limited transcutaneous absorption (see CLINICAL PHARMACOLOGY).

DOSAGE AND ADMINISTRATION

Apply sufficient quantity to adequately cover all lesions every 3 hours, six times per day for 7 days. The dose size per application will vary depending upon the total lesion area but should approximate a one-half inch ribbon of ointment per 4 square inches of surface area. A finger cot or rubber glove should be used when applying ZOVIRAX to prevent autoinoculation of other body sites and transmission of infection to other persons. **Therapy should be initiated as early as possible following onset of signs and symptoms.**

HOW SUPPLIED

ZOVIRAX Ointment 5% is supplied in 15-g tubes (NDC 0173-0993-94) and 3-g tubes (NDC 0173-0993-41). Each gram contains 50 mg acyclovir in a polyethylene glycol base. **Store at 15° to 25°C (59° to 77°F) in a dry place.**

ANIMAL PHARMACOLOGY AND ANIMAL TOXICOLOGY

Topical treatment of guinea pigs with 10% acyclovir in polyethylene glycol ointment for 3 weeks did not result in cutaneous irritation or systemic toxicity. Also, a wide variety f animal tests by parenteral routes demonstrated that acylovir has a low order of toxicity.

cyclovir did not cause dermal sensitization in guinea pigs.

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• Data on file at Glaxo Wellcome Inc.